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Heritability of Ambulatory and Beat-to-Beat Office Blood Pressure in Large Multigenerational Arab Pedigrees: The 'Oman Family Study'

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Objective: To estimate the heritability of ambulatory blood pressure (BP), heart rate (HR), and beat-to-beat office BP and HR in an isolated, environmentally and genetically homogeneous Omani Arab population. *Methods:* Ambulatory BP measurements were recorded in 1,124 subjects with a mean age of 33.8 ± 16.2 years, using the auscultatory mode of the validated Schiller ambulatory BP Monitor. Beat-to-beat BP and HR were recorded by the Task Force Monitor. Heritability was estimated using quantitative genetic analysis. This was achieved by applying the maximum-likelihood-based variance decomposition method implemented in SOLAR software. *Results:* We detected statistically significant heritability estimates for office beat-to-beat, 24-hour, daytime, and sleep HR of 0.31, 0.21, 0.20, and 0.07, respectively. Heritability estimates in the abovementioned conditions for systolic BP (SBP)/diastolic BP (DBP)/mean BP (MBP) were all significant and estimated at 0.19/0.19/0.19, 0.30/0.44/0.41, 0.28/0.38/0.39, and 0.21/0.18/0.20, respectively. Heritability estimates for 24-hour and daytime ambulatory SBP, DBP, and MBP ranged from 0.28 to 0.44, and were higher than the heritability estimates for beat-to-beat recordings and sleep periods, which were estimated within a narrow range of 0.18–0.21. *Conclusion:* In this cohort, because shared environments are common to all, the environmental influence that occurs is primarily due to the variation in non-shared environment that is unique to the individual. We demonstrated significant heritability estimates for both beat-to-beat office and ambulatory BP and HR recordings, but 24-hour and daytime ambulatory heritabilities are higher than those from beat-to-beat resting levels and ambulatory night-time recordings.

■ **Keywords:** ambulatory blood pressure, beat-to-beat blood pressure, heritability, Omani pedigrees

Epidemiological evidence has shown hypertension to be a complex disease resulting from the interaction of genetic and environmental factors (Harrap, 1994; Stamler et al., 1975; Ward, 1990; Williams et al., 1991). Studies on twins, large cohorts, and isolated pedigrees have provided more insight into understanding complex traits of hypertension compared with case–control association studies (Hiekkalinna et al., 2012; Wang et al., 2011; Wu et al., 2010). In addition, genetic studies using ambulatory blood pressure (BP) measurements as a phenotype were found to be potentially more powerful than those using office BP measured in the clinic (Fava et al., 2004; Kotchen et al., 2000; Kupper et al., 2005; Tomaszewski et al., 2010; Wang et al., 2009). A distinct advantage is that ambulatory recordings allow collection of multiple day and night values in a natural setting. Furthermore, ambulatory BP is unaffected by the 'white-coat' effect (Tomaszewski et al., 2010) and is a better predictor of target organ damage (Verdecchia et al., 2001).

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Most heritability studies on ambulatory BP were conducted in twins and have reported high heritability estimates. Studies in different cohorts of twins of Caucasian and African origins reported heritability estimates for systolic BP (SBP) and diastolic BP (DBP) during 24-hour, daytime, and night (sleep) time ranging from 0.44 to 0.75 (Fagard et al., 1995; Kupper et al., 2005; Wang et al., 2009; 2011).

To date, only three family studies reported heritability estimates for ambulatory BP. In 260 siblings from 118 Swedish families, Fava et al. (2004) reported significant heritability estimates of 0.30 for SBP, 0.29 for DBP, and 0.24 for mean BP (MBP) for 24-hour ambulatory BP; for daytime ambulatory BP these estimates were 0.33 (SBP), 0.22 (DBP), and 0.19 (MBP), while for night-time ambulatory BP they were 0.37 (SBP), 0.32 (DBP), and 0.32 (MBP). No significant heritability estimates for office BP were found. In a cohort of 314 subjects from East African families, with at least two hypertensive siblings, Bochud et al. (2005) reported heritability estimates of 0.37 and 0.24, for daytime SBP and DBP, and 0.34 and 0.37 for sleep SBP and DBP, respectively. Heritability estimates for office SBP and DBP were 0.20 and 0.05, respectively. Tomaszewski et al. (2010) measured 24-hour ambulatory BP in more than 2,000 individuals, recruited as part of the Genetic Regulation of Arterial Pressure of Humans in the Community (GRAPHIC) family study consisting of nuclear families (all of white European ancestry) with both parents (aged 40–60 years) and two adult offspring (aged ≥18 years) that were identified through general practices in Leicestershire, United Kingdom. They found that the heritability of mean 24-hour SBP (0.33) was marginally higher than the clinic SBP (0.31), but the mean 24-hour DBP heritability (0.41) was significantly higher than the heritability of clinic DBP (0.32).

In our Oman Family Study (OFS; Hassan et al., 2005), which began in 2002, we combined the advantages of unique homogeneous Arab pedigrees with extensive phenotyping of more than 215 BP hemodynamic and related phenotypes at rest and during laboratory physical and mental stress, detailed heritabilities of which were reported elsewhere (Bayoumi et al., 2007; Hassan et al., 2009).

In this study, we report and compare heritability estimates of ambulatory BP and HR measurements with those from beat-to-beat office BP and HR in this isolated, environmentally and genetically homogeneous population.

Methods and Study Design

Study Area and Pedigrees

Pedigrees. Five large, extended, and highly consanguineous families, each living in a separate village, were selected within a perimeter of 20 km around the city of Nizwa (Table 1). The number of subjects interviewed and found eligible for the study from the five pedigrees was 327, 160, 230, 279, and 281, totaling 1,277, which represented approximately 10–15% of the total number of individuals in these five pedigrees. They were 16–80 years old and all voluntarily took part in the study, appeared healthy, and had no clinical complaints, as determined by a questionnaire. First-cousin marriages represent >50% of all marriages. Polygamy is widely practiced, with some men marrying up to four wives (Sulaiman et al., 2001). The consequent rapid population growth produced young isolates of 7–12 generations each. A more detailed description of the cohort stratification and the OFS design can be found in earlier reports (Bochud et al., 2005). Hypertension was diagnosed when subjects had a 24-hour SBP and/or DBP ≥135/85 mmHg (Pickering et al., 2005) or when they were on antihypertensive treatment. The prevalence of hypertension was 20% (males 22% and females 18%) with 2% of both genders on medication. Subjects were allowed to continue with their anti-hypertensive medication, coronary vasodilators, antiplatelet agents, and lipid-lowering drugs. Exclusion criteria were pregnancy, malignancy, renal failure, heart failure, and myocardial infarction/stroke within 6 months. A written and signed or thumb-print rubber-stamped consent was obtained from each subject. The study was approved by the Medical Research and Ethics Committee of Sultan Qaboos University.

TABLE 1

Type and Size of Relative Pairs in the Five Pedigrees

Relationship	Size
Pedigree members	1,851
Parent–offspring	2,482
Siblings	1,278
Grandparent–grandchild	3,774
Avuncular	2,815
Half-siblings	322
Grand avuncular	2,928
Half avuncular	918
First cousins	2,610
First cousins, 1 removed	932
Half first cousins, 1 removed	441
Second cousins	4,363
Other relationships	390
Total	25,104

Anthropometric measurements. Height, weight, and waist circumference were measured at home using standard methods. Body mass index (BMI) was calculated as weight/height^2. Body fat percentage was estimated using electrical impedance (Tanita, Japan).

Ambulatory Blood Pressure Measurements

Ambulatory BP measurements were recorded during the course of a whole day on the first home visit in 1,124 subjects with a mean age of 33.8 ± 16.2 years, using the auscultatory mode of the validated Schiller BR 102 ambulatory BP monitor (O'Brien et al., 1999). With the subject seated, the appropriate size cuff was fixed to the non-dominant arm by male and female technicians, who explained the procedure separately to male and female subjects. The procedures used by

the two technicians were matched for cuff and microphone positioning. Three BP readings were also taken during the same period with a calibrated mercury sphygmomanometer on the dominant arm. Recordings were accepted when the average of both measurement methods did not differ by >5 mmHg. These measurements were not used as phenotypes. To reduce movement artifacts during ambulatory BP recordings, subjects were discouraged from strenuous physical activity and were asked to remain as motionless as possible during the inflation and deflation periods. They were also instructed to record their activity, position, location, time of going to bed, and time of awakening in a diary. Illiterate subjects (5% of elderly males and 60% of elderly females) were assisted by their children or husbands. The BP monitor was programmed to record BP every 30 minutes from 07:30 to 21:30 and every 60 minutes from 21:30 to 09:30, with a total of 26 hours. The first 2 hours of monitoring were considered as an adaptation period and were not included in the calculation of BP means. Recordings were accepted as valid when the rate of artifacts was <25% and when the recording lasted for at least 20 consecutive hours. Data output from the 24-hour monitor for HR, SBP, DBP, and MBP was edited by one technician, trained at identifying artifacts and outliers. MBP was automatically calculated by the monitor as (DBP + 1/3rd pulse pressure). The daytime and sleep periods were determined for each subject according to their actual waking and sleeping time as recorded in their diaries. The average HR and BP levels during the24 hours and during daytime and sleep periods were calculated.

Sleep quality was scored by each subject using a scale of 0–3, referring to the number of times the subject was awakened by the cuff inflation: 0: *sound asleep*; 1: *awoken once*; 2: *awoken twice*; and 3: *awoken three times or more*. Subjects with a score of 3 had their ambulatory monitoring repeated and those who had the same score (6%) after the second measurements were excluded from the study. Valid measurements were obtained in 1,124 (88%) of total subjects.

Beat-to-Beat Blood Pressure and Heart Rate Recordings

Subjects reported to the field research center clinic at 07:00 a.m. with the ambulatory BP monitor still recording. After removing the ambulatory BP monitor and explanation of the office beat-to-beat procedure, ECG electrodes, as well as finger and upper arm cuffs of the Task Force Monitor (TFM, CNSystems, Austria), were attached and the subjects were made to rest in supine position for 10 minutes on a comfortable bed, in a quiet office with a temperature between 24 and 26°C. Measurements were acquired for the subsequent 10 minutes.

HR was obtained from lead 2 of a 6-lead ECG and the beat-to-beat BP was recorded using the vascular unloading technique, whereby finger cuff readings were recorded, automatically counterchecked, and corrected every minute by the oscillometric BP measurements recorded from the contra-lateral upper arm. These upper-arm cuff measurements were computed by the TFM monitor to adjust any errors of finger cuff beat-to-beat measurements, but they were not included as phenotypes in the current study. The TFM monitor displayed beat-to-beat BP and HR with their average values in graphical and digital format (Fortin et al., 2006; Gratze et al., 1998; Parati et al., 2003).

Statistics. Beat-to-beat measurements for HR and BP, as well as 24-hour, daytime, and night-time ambulatory measurements, were averaged. Descriptive and comparative analyses were performed using the SPSS software package (IBM Corporation New York, USA).

Quantitative genetic analysis was performed utilizing the maximum-likelihood-based variance decomposition method implemented by the Sequential Oligogenic Linkage Analysis Routines (SOLAR, San Antonio TX USA; Beaty & Liang, 1987) software program. Table 1 shows the total number of relative pairs used in the analysis. Heritability, defined as the proportion of the phenotypic variance attributed to additive genetic effects, is estimated as

$$h^2 = \sigma^2_G/\sigma^2_P,$$

where $\sigma^2{}_G$ is the additive genetic variance and $\sigma^2{}_P$ is the phenotypic variance.

The significance of h^2 was determined by using the likelihood ratio test. The null hypothesis of additive genetic variance equal to zero was tested against an alternative hypothesis in which the additive genetic variance was estimated. Twice, the difference in logarithmic likelihoods was distributed asymptotically as a $^1/_2$:$^1/_2$ mixture of a χ^2 variable, with one degrees of freedom and a point of mass at zero (Beaty & Liang, 1987). Age, sex, and their higher-order terms and interactions (i.e., age^2, age × sex, and age^2 × sex) were included as covariates in the model, irrespective of their statistical significance.

Results

Table 2 shows the characteristics of the population (mean age of 33.8 years): Females had similar waist circumference and BMI as males, but significantly higher percentage body fat than males. Table 3 shows the comparisons between ambulatory daytime and sleep HR, SBP, DBP, and MBP measurements and their respective office beat-to-beat measurements. In males, all daytime values were significantly higher, while their sleep values were significantly lower than their respective beat-to-beat values. However, in females, daytime values were significantly higher than beat-to-beat values, while during sleep only HR, not BP, values were significantly lower than beat-to-beat resting values.

Table 4 shows the univariate results of the heritability estimates, 95% confidence intervals (CI), and significance

TABLE 2

General and Anthropometric Characteristics of the Population and Their Gender Differences

Variables	Total ($n = 1,124$)	Males ($n = 506$)	Females ($n = 618$)	p
Age (years)	33.8 (16.2)	33.0 (17.0)	34.5 (15.5)	<.005
Waist circumference (cm)	81.0 (14.5)	81.1 (14.3)	80.0 (14.6)	NS
Height (cm)	158.3 (9.3)	165.8 (7.3)	152.2 (5.5)	<.001
Weight (kg)	62.9 (14.6)	68.1 (14.4)	58.7 (13.4)	<.001
BMI (kg/m^2)	25.1 (5.4)	24.8 (5.0)	25.7 (5.7)	NS
Body fat (%)	23.5 (10.5)	17.9 (8.4)	28.1 (9.8)	<.001

Note: Values represent means (±*SD*). NS = not significant.

TABLE 3

Comparisons of Beat-to-Beat, Daytime and Sleep Heart Rate, Systolic, Diastolic, and Mean Blood Pressure Among Males and Females

	Males ($n = 506$)			Females ($n = 618$)		
Variable	Rest (b-b)	Daytime (ABP)	Sleep (ABP)	Rest (b-b)	Daytime (ABP)	Sleep (ABP)
HR	67.8 (10.0)*†	80.7(9.6)†	64.7 (11.7)	73.8 (10.7)*†	84.5 (10.0)†	70.2 (10.0)
SBP	118.7 (15.4)*†	129.7 (14.1)†	110.9 (14.7)	107.6 (13.1)*†	120.8 (12.8)†	107.2 (15.6)
DBP	76.2 (12.2)*†	83.6 (10.5)†	69.2 (12.2)	67.4 (10.1)*	78.0 (7.1)†	67.3 (11.1)
MBP	89.4 (13.4)*†	99.7 (11.1)†	83.2 (12.4)	78.3 (10.7)*	94.5 (10.4)†	80.3 (11.8)

Note: HR = heart rate; SBP = systolic BP; DBP = diastolic BP; MBP = mean BP; b-b = beat-to-beat; ABP = ambulatory BP.
Values are mean (±*SD*).
*Significant difference with daytime values.
†Significant difference with sleep values ($p < .05$).

TABLE 4

Heritabilities of Heart Rate, Systolic, Diastolic, and Mean BP Measured Beat-to-Beat in the Office and Using Ambulatory BP Monitoring

	h^2 (±95% CI)	p	Proportion of variance due to covariates*
Office resting beat-to-beat			
HR	0.31 (0.20–0.42)	6.6×10^{-17}	37.2
SBP	0.19 (0.08–0.30)	3.8×10^{-6}	18.0
DBP	0.19 (0.09–0.29)	1.2×10^{-6}	21.1
MBP	0.19 (0.09–0.29)	1.0×10^{-6}	21.2
ABP total 24 hours			
HR	0.21 (0.11–0.31)	2.9×10^{-10}	6.7
SBP	0.30 (0.19–0.41)	1.4×10^{-18}	19.5
DBP	0.44 (0.33–0.55)	3.0×10^{-31}	11.1
MBP	0.41 (0.30–0.52)	9.7×10^{-29}	14.2
ABP daytime period			
HR	0.20 (0.10–0.30)	9.4×10^{-10}	8.0
SBP	0.28 (0.18–0.38)	2.0×10^{-18}	15.5
DBP	0.38 (0.28–0.48)	2.6×10^{-29}	6.6
MBP	0.39 (0.29–0.49)	1.2×10^{-31}	9.0
ABP sleep period			
HR	0.07 (0.01–0.15)	0.011	7.2
SBP	0.21 (0.11–0.31)	2.1×10^{-8}	19.5
DBP	0.18 (0.08–0.28)	1.8×10^{-6}	15.7
MBP	0.20 (0.10–0.30)	1×10^{-7}	16.8

Note: HR = heart rate; SBP = systolic BP; DBP = diastolic BP; MBP = mean BP; h^2 = Heritability; 95% CI = 95% confidence interval; ABP = ambulatory BP.
*Models were adjusted for age, sex, age^2, age × sex, and age^2 × sex.

levels and proportion of variance due to covariates for resting office beat-to-beat, total 24-hour, daytime, and sleep HR, SBP, DBP, and MBP. Heritability estimates for resting laboratory beat-to-beat, 24-hour, daytime, and sleep HR were 0.31, 0.21, 0.20, and 0.07, respectively. Heritability estimates for the previously mentioned conditions for SBP/DBP/MBP were 0.19/0.19/0.19, 0.30/0.44/0.41, 0.28/0.38/0.39, and 0.21/0.18/0.20, respectively. Note that heritability for SBP, DBP, and MBP for ambulatory 24-hour and daytime measures ranged from 0.28 to 0.44. These values were close to each other and higher than their respective heritability estimates for beat-to-beat measurements and for the sleep period. That is, their 95% CI showed little overlap. In contrast, heritability estimates for resting beat-to-beat and for sleep SBP, DBP, and MBP had a narrow range of 0.18–0.21.

Discussion

The study was conducted in an isolated, highly consanguineous, and multigenerational Arab pedigree of 1,124 individuals, with a mean age of 33.8 years, 60% of whom were younger than 30 years. The strengths of the OFS include the accessibility and authenticity of their genealogical records; the close family ties of all five pedigrees, which in turn guaranteed a more homogeneous environmental exposure with similar socioeconomic status and congruent health-related habits such as diet, habitual physical activity; and the strict religious abstinence from alcohol and smoking (Bayoumi et al., 2007; Hassan et al., 2009).

In this study, we detected significant effects of additive genetic factors for ambulatory HR and BP measures using univariate analysis. The most important findings of this study were (1) statistically significant heritability estimates for ambulatory 24-hour, HR, SBP, DBP, and MBP, which were close to their respective daytime values (0.28–0.44), while heritability estimates for sleep values were close to their respective office resting beat-to-beat values (0.18–0.21); and (2) heritability estimates of beat-to-beat HR and

BP during resting office conditions were lower than their respective daytime ambulatory values.

To our knowledge, only three family studies reported heritability estimates of ambulatory BP (Bochud et al., 2005; Fava et al., 2004; Tomaszewski et al., 2010). Although these studies were conducted in ethnically different populations, Fava et al. (2004) reported somewhat lower heritability estimates for 24-hour and daytime ambulatory BP, whereas heritabilities for the sleep period were somewhat higher than those found in our study; heritability estimates for the 24-hours in Tomaszewski et al. (2010) were comparable with our study, while Bochud et al. (2005) reported higher heritabilities during sleep than the OFS did. The findings of OFS and other previous studies confirm the findings of Kotchen et al. (2000), who found higher heritability estimates for multiple BP measurements averaged over 24 hours compared with single BP measurements in black sibpairs. To estimate heritabilities for multiple traits, we recorded an average of 700 measurements in 10 minutes during absolute resting conditions. Heritability estimates of beat-to-beat BP were not different from heritabilities of office BP in Bochud et al. (2005), but were lower than daytime ambulatory BP values in OFS. Our study indicates that the number of BP readings over 24 hours in real-life situations increased the heritability estimates compared with hundreds of recordings over a short period of time in quiet laboratory conditions. Potentially, these 10-minute beat-to-beat registrations might still be occasion-specific, whereas the ambulatory BP might give a better reflection of the stable average BP of a person across the day in different circumstances. In addition, within the same population, we recently reported quantitative trait loci from linkage results of beat-to-beat BP under resting and stressful laboratory stress conditions (Hassan et al., 2011). All the significant loci with Logarithm of Odds (LOD) scores > 3 were observed for SBP, DBP, and MBP during mental stress. Beat-to-beat BP readings obtained during mental stress over 3 minutes are perhaps more akin to real-life ambulatory BP recordings obtained in this and other studies.

In recent work, Wang et al. (2009; 2011) highlighted the advantages of ambulatory over office BP measurements in gene-finding studies and showed that daytime and nighttime BP are influenced by partly different genes and that the genes underlying 24-hour BP also differ from those for office BP.

In OFS, we did not exclude treated and untreated hypertensive subjects as other twin and family studies did (Bochud et al., 2005; Kupper et al., 2005), because these studies suggested that exclusion of medicated and unmedicated hypertensive subject groups may have reduced heritability estimates, leading to lower power in gene-finding studies.

A potential limitation of this study compared with the one by Kotchen et al. (2000) was that we did not measure ambulatory BP in the office where, aside from being in an environment setting different from a clinical one, both upper arms are used by the cuffs of the impedance unit (TFM). Our study aimed to reduce the number of procedures taken during the short time period when subjects were in the office. In addition, the landscape of BP genetic research is dominated by office mercury sphygmomanometer BP based on a limited number (1–3) of measurements, which have their limitations compared with ambulatory BP measurements conducted in a real-life setting.

We would like to caution that due to the homogeneous, young aged, inbred, and ethnically specific character of the population studied, our results should be interpreted with care when compared with other population groups.

We conclude that in this cohort, as the environment is shared and therefore common to all, the environmental influence that does occur is primarily due to the variation of non-shared environments that are unique to the individual. We demonstrated significant heritability estimates for both beat-to-beat office and ambulatory BP and HR recordings, but 24-hour and daytime ambulatory heritabilities are higher than those from beat-to-beat resting levels and ambulatory night-time recordings.

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